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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,273	12/13/1999	JORJ TERRY ULRICH	9950-0002	5731

23980 7590 05/05/2004

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 05032004

Application Number: 09/402,273
Filing Date: December 13, 1999
Appellant(s): ULRICH ET AL.

Karen Canaan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/15/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: The written description rejection of claims 1-2, 6-8 and 15-23 under 35 U.S.C. § 112, first paragraph is hereby withdrawn.

The issues on appeal are as follow:

A. Whether the primary reference WO96/34626 is disqualified as prior art under 35 U.S.C. § 103(a).

B. claims 1-2, 6-8, 15-17, and 19-23 under 35 U.S.C. § 103(a) as obvious over WO 96/34626 in view of WO 92/16556, and U.S. Patent No. 5,795,862;

C. claim 18 under 35 U.S.C. § 103(a) as obvious over WO 96/34626 in view of WO 92/16556 and U.S. Patent No. 5,795,862 as applied to claims 1-2, 6-8, 15-17, and 19-23 and further in view of Marsh; WO 92/16556; U.S. Patent No. 5,750,1 10; and Hoyne et al.; and

D. claims 1 and 23 under 35 U.S.C. § 103(a) as obvious over WO 96/34626 in view of Holen et al.; WO 92/16556; U.S. Patent No. 5,750,1 10; and Hoyne et al.

(7) Grouping of Claims

Appellant's brief includes a statement that all claims stand and fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

WO 96/34626	WHEELER	11-1996
WO 92/16556	VANWIJNENDALE	10-1992
5,795,862	FRANK	8-1998
5,750,110	FRIEELS	5-1998

Marsh et al, Int. Arch. Allergy 41(1): 199-215, 1971

Hoyne et al, Immunology and Cell Biology 74: 180-186, April 1996

Holen et al, Clin Exp Allergy 26(9): 1080-8, September 1996

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-2, 6-8, 15-17, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892).

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine in combination with a modified allergen or allergen extracts of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches the reference pharmaceutical composition was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

The claimed invention differs from the teachings of the reference in that the pharmaceutical composition comprises a 3-DMPL that selectively enhances TH_1 over TH_2 response and the allergen or allergen extract(s) is not modified.

The WO 92/16556 publication teaches 3D-MPL is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) and is from Ribi (see page 24, line 23, in particular). The reference adjuvant is useful for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH), which is a TH1 immune response (See page 29, lines 8-16, in particular).

The '862 patent teaches a therapeutic composition comprising unmodified allergen of isolated flea saliva protein and the Ribi adjuvant from Ribi ImmunoChem enhances the immune response to any antigen (See column 42, line 20-35, claims 22 and 24 of '862, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant (WO 92/16556 publication) in a pharmaceutical composition comprising tyrosine and modified allergen for desensitization therapy as taught by the WO/9634626 publication or unmodified allergen as taught by the '862 patent for a pharmaceutical composition that enhances the TH1 responses. From the combined

teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the references because the WO 92/16556 publication teaches that the adjuvant formulations containing 3D-MPL are able to induce specific T cell responses such as effector cell mediated (DTH) immune response where DTH is a TH_1 response (See page 29, lines 8-16, in particular). The WO/9634626 publication teaches the reference pharmaceutical composition was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular). The '862 patent teaches unmodified allergen and adjuvant such as Ribi adjuvant is useful in desensitization therapy because it enhances the host immune response to any allergen (See claims 22 and 25 of '862 patent, column 4, lines 19-21 and 30-33, sentence spanning from column 7 bridging column 8, in particular). *In re Kerkhoven*, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). Claim 16 is included in this rejection because glutaraldehyde is a species of dialdehyde. The recitation of unmodified allergen or allergen extract(s) is an obvious variation of the teachings of the WO 96/34626 publication because all initial crosslinked (modified) allergen or allergen extract(s) are all start out with unmodified allergen or allergen extract(s). The enhancing TH1 response over a TH2 response in claim 1 is an inherent functional property of the reference 3-DMPL adjuvant. The inherent functional property of a compound cannot be separated from the compound.

2. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892) as applied to claims 1-2, 6-8, and 15-17 and 19-23 mentioned above and further in view of Marsh et al (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892).

The combined teachings of the WO 96/34626 publication, the WO 92/16556 publication and the '862 patent have been discussed supra.

The claimed invention in claim 18 differs from the combined teachings of the references only in that the composition of the allergen or allergen extract(s) is not modified by reaction with a crosslinking agent.

Marsh *et al* teach unmodified native allergen such as pollen allergen and chemically modified such as formalinized allergen (See page 202, Antigenicity and Allergenicity, second paragraph from the bottom, in particular).

The '110 patent teaches various vaccine compositions comprising 3De-acylated monophosphoryla lipid A (3-DMPL), also known as GB2220 211 (See column 1, lines 11-14, in particular). The '110 patent further teaches that a combination of adjuvant such as 3D-MPL and QS21 synergy the production of CTL and gamma interferon response more than twice the sum of individual response while each adjuvant on its own induces cells capable of secreting IFNγ in response to any antigen such as rgD2t (See column 5, lines 16-22, in particular).

Hoyne *et al* teach T helper 1 (Th1) cells preferentially secrete cytokines (i.e., IFN-γ) whereas Th2 cells preferentially secrete IL-4 and IL-10. The IFN-γ secreted by Th1 cells is known to inhibit growth and differentiation of T helper 2 (Th2) cells and vice versa (See page 180, column 1, Introduction, in particular). Hoyne *et al* teach allergen-specific T cells isolated from atoptic patients show a high level of IL-4 and a low level of IFN-γ (See page 180, column 1, first paragraph, in particular) and patients who have been desensitized normally display a decrease in Th2 immune responses. Clinical improvement in allergic patients correlates with a decrease in immediate and late phase skin reactivity with a long-term rise in IgG4 levels and a decrease in allergen specific IgE (See page 183, column 1, last paragraph, in particular). Hoyne *et al* further teach that a major key to successful immunotherapy depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells leads to clinical improvement usually correlates with a decrease in allergen specific IgE, a decrease in immediate and late phase skin reactivity and a rise in IgG4 level in human or IgG2a or IgG2b in mouse (See page 183, column 2, last paragraph, in particular). Vaccination under conditions such as co-administering allergen in the presence of IFN-γ to promote Th1 responses instead of Th2 responses may reprogrammed the immune response to prevent allergic sensitization (See abstract, page 183, column 2, Future directions, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant as taught by the '110 patent or the WO 92/16556 publication in a pharmaceutical composition comprising tyrosine, modified or

unmodified allergen or allergen extract(s) as taught by the WO 96/34626 publication as taught by the '892 patent or Marsh *et al* for a pharmaceutical composition that would have selectively enhanced a TH1 response over a TH2 response as taught by Hoyne *et al* and the'110 patent. From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the references because Hoyne *et al* teach that a major key to successful immunotherapy depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells would have been expected to improve clinical symptoms, a result in alleviation of observable/measurable clinical symptoms such as immediate and late phase skin reactivity (See page 183, column 2, second paragraph, in particular). The WO 92/16556 publication teaches 3D-MPL adjuvant is able to induce specific T cell responses such as an effector cell mediated (DTH) immune response, which is a TH1 response (See page 29, lines 8-16, in particular). The '110 patent teaches that individual adjuvants such as 3D-MPL and QS21 increase gamma interferon production (Th1 response), however, a combination of adjuvants such as 3D-MPL and QS21 are synergistic for production of CTL and gamma interferon responses more than twice the sum of individual response (See column 5, lines 16-22, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized allergen that is for desensitization therapy of allergy sufferers because glutaraldehyde modified allergen reduces the allergenicity of said allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

3. Claims 1 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of Holen *et al* (Clin Exp Allergy 26(9):1080-8, Sept 1996; PTO 892), WO 92/16556 (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892).

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine combined with a modified allergen or allergen extract(s) of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen

(See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized pollen allergen was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

The invention of claim 1 differs from the teachings of the reference in that the pharmaceutical composition selectively enhances a TH1 response over a TH2 response comprising 3-DMPL.

The invention of claim 23 differs from the teachings of the reference only in that the composition of allergen or allergen extracts is ovalbumin.

Holen *et al* teach proteins of hen egg whites are common ingredients in food and difficult to eliminate. Allergens of egg white induce allergic symptoms among relatively high number of patients suffering from food allergy. Holen *et al* teach human T cells from allergic patients recognized several allergens such as ovomucoid, lysozyme and ovalbumin and epitopes within the ovalbumin such as 105-122 and 323-339 (see abstract, in particular). Ovomucoid and ovalbumin induced allergen specific IgE synthesis by even a small fraction of B cells present in the ovalbumin and ovomucoid specific T cell lines. Holen *et al* further teach that OA peptides 105-122 and 323-339 have no affinity to the specific IgE of the two patients, which could be useful for peptide-based immunotherapy.

The WO 92/16556 publication teaches 3D-MPL is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) and is from Ribi (see page 24, line 23, in particular). The reference adjuvant is useful for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH), which is a TH1 immune response (See page 29, lines 8-16, in particular).

The '110 patent teaches various vaccine compositions comprising 3De-acylated monophosphoryl lipid A (3-DMPL), also known as GB2220 211 (See column 1, lines 11-14, in particular). The '110 patent teaches that individual adjuvants such as 3D-MPL and QS21 increase gamma interferon production, however, a combination of adjuvants such as 3D-MPL and QS21 are synergistic for production of CTL and gamma interferon responses more than twice the sum of individual response (See column 5, lines 16-22, in particular).

Hoyne *et al* teach T helper 1 (Th1) cells preferentially secrete cytokines (i.e., IFN-γ) whereas Th2 cells preferentially secrete IL-4 and IL-10. The IFN-γ secreted by Th1 cells is known to inhibit growth and differentiation of T helper 2 (Th2) cells and vice versa (See page 180, column 1, Introduction, in particular). Hoyne *et al* teach allergen-specific T cells isolated from atoptic patients show a high level of IL-4 and a low level of IFN-γ (See page 180, column 1, first paragraph, in particular) and patients who have been desensitized normally display a decrease in Th2 immune responses. Clinical improvement in allergic patients correlates with a decrease in immediate and late phase skin reactivity with a long-term rise in IgG4 levels and a decrease in allergen specific IgE (See page 183, column 1, last paragraph, in particular). Hoyne *et al* further teach that a major key to successful immunotherapy depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells leads to clinical improvement usually correlates with a decrease in allergen specific IgE, a decrease in immediate and late phase skin reactivity and a rise in IgG4 level in human or IgG2a or IgG2b in mouse (See page 183, column 2, last paragraph, in particular). Vaccination under conditions such as co-administering allergen in the presence of IFN-γ to promote Th1 responses instead of Th2 responses may reprogrammed the immune response to prevent allergic sensitization (See abstract, page 183, column 2, Future directions, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the allergen or allergen extract(s) as taught by the WO 96/34626 publication for the ovalbumin as taught by the Holen *et al* in a pharmaceutical composition comprising tyrosine and ovalbumin in combination with adjuvant such as 3-DMPL that is capable of enhancing a Th1 response over a TH2 response as taught by the WO 92/16556 publication, the '110 patent and Hoyne *et al.* From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the references because Holen *et al* teach ovalbumin is one of the allergens in egg white that induces allergic symptoms by increasing allergen specific IgE synthesis among relatively high number of patients suffering from food allergy (see abstract, in particular). The WO 92/16556 publication teaches that the adjuvant formulations containing 3D-MPL induce specific T cell responses such as a DTH immune response, which is a TH1 response (See page 29, lines 8-16, in particular). Hoyne *et al* teach that a major key to successful immunotherapy

depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells leads to clinical improvement usually correlates with a decrease in allergen specific IgE, a decrease in immediate and late phase skin reactivity and a rise in IgG4 level in human (See page 183, column 2, last paragraph, in particular). Vaccination under conditions such as co-administering allergen in the presence of IFN-γ to promote Th1 responses instead of Th2 responses may reprogrammed the immune response to prevent allergic sensitization (See abstract, page 183, column 2, Future directions, in particular). The '110 patent teaches that individual adjuvants such as 3D-MPL and QS21 increase gamma interferon production, which is a Th1 response (See column 5, lines 16-22, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized pollen allergen was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

(11) Response to Argument

Claims Rejection - 35 USC § 103

Claims 1-2, 6-8, 15-17, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892).

At page 19-22 of the Brief, Appellant submits that the primary reference WO96/34626, which has international publication date of November 7, 1996 and an international filing date of April 25, 1996. Pursuant to 35 U.S.C. § 102(a), the effective date of the WO 96/34626 reference is its international publication date. Accordingly, under 35 U.S.C. § 103(a), proof of invention prior to effective date of the WO96/34626 reference will serve to disqualify this reference as prior art to instant application. The attached Declaration of Alan Worland Wheeler under 37 C.F.R. § 1.131 is enclosed in Appendix C.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

In response to appellant's argument that the WO96/34626 publication is disqualified as prior art, the WO96/34626 reference was published November 1996, which is more than one year

prior to the effective filing date 4/3/1998 of the present application. The WO96/34626 reference is a statutory bar under 35 U.S.C. 102(b) and thus cannot be overcome by declaration under 37 CFR 1.131.

At page 22 second paragraph of the Brief, Appellant submits that WO 92/16556 does not teach or suggest that the 3-DMPL is being used as an adjuvant to induce a Th1 response; rather, WO92/16556 teaches that the 3-DMPL is used as an adjuvant to "present immunogens effectively to the host immune system such that both arms of the immune response (neutralizing antibody and effector cell mediated immunity (DHT) are produced" (p. 8, paragraph 22-26).

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

Claim 1 recites a pharmaceutical composition capable of selectively enhancing a T helper 1 (Th1) response over a T helper 2 response (Th2) comprising tyrosine, an allergen or allergen extract(s), and 3-DMPL. The WO92/16556 does not teach neutralizing antibody is equivalent to T helper cell type 2 immune response as asserted by Appellant. In fact, the WO 92/16556 publication teaches 3D-MPL or 3D monophosphoryl lipid A is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) that stimulates specific T cell responses such as effector cell mediated immunity (DTH) which is a T helper cell type 1 response (See page 29, lines 8-16, in particular). The reference adjuvant 3D-MPL is from Ribi (see page 24, line 23, in particular). The Th1 response was known at the time the invention was made to stimulate T cells to secrete cytokine such as IFNγ (cross inhibits Th2 response of production of IL4, and IL-10). In fact, Hoyne *et al*, of record, teach Th1 cells preferentially secrete cytokine such as IFN-γ whereas Th2 cells preferentially secrete IL-4 and IL-10; The IFN-γ secreted by Th1 cells can inhibit the growth and differentiation of Th2 cells and vice versa (See page 180, column 1, Introduction, in particular). In order to assume that the humoral response (antibody response) is a Th2 response taught by the WO92/16556, the WO92/16556 publication must teach that reference antibody is IgG1 type which is indicative of Th2 immune response as defined in page 5, line 16 of instant specification. The WO92/16556 publication is silent on the matter that the antibody (humoral) response is IgG1 type. Given the DTH response induced by the reference 3-DMPL, the reference humoral or antibody response would have been expected to be IgG2a or IgG2b subtype in the mouse, which is indicative of Th1 response. Further, the functional property of enhancing

effector cell mediated immunity (DTH) or Th1 response of 3-DMPL taught by the WO9216556 cannot be separated from the product.

At page 23 first paragraph of the Brief, Appellant submits that the WO 92/16556 publication was not intended for use with an allergen or allergen extract(s) and the reference does not contemplate the use of tyrosine in combination with 3-DMPL for any purpose.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller* , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine in combination with a modified allergen or allergen extracts of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches the reference pharmaceutical composition was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

The claimed invention differs from the teachings of the reference in that the pharmaceutical composition comprises a 3-DMPL that selectively enhances TH_1 over TH_2 response and the allergen or allergen extract(s) is not modified.

The WO 92/16556 publication teaches 3D-MPL is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) and is from Ribi (see page 24, line 23, in particular). The reference adjuvant is useful for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH), which is a TH1 immune response (See page 29, lines 8-16, in particular).

The '862 patent teaches a therapeutic composition comprising unmodified allergen of isolated flea saliva protein and the Ribi adjuvant from Ribi ImmunoChem enhances the immune response to any antigen (See column 42, line 20-35, claims 22 and 24 of '862, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant (WO 92/16556 publication) in a pharmaceutical composition comprising tyrosine and modified allergen for desensitization therapy as taught by the WO/9634626 publication or unmodified allergen as taught by the '862 patent for a pharmaceutical composition that enhances the TH1 responses. From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the references because the WO 92/16556 publication teaches that the adjuvant formulations containing 3D-MPL are able to induce specific T cell responses such as effector cell mediated (DTH) immune response where DTH is a TH_1 response (See page 29, lines 8-16, in particular). The WO/9634626 publication teaches the reference pharmaceutical composition was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular). The '862 patent teaches unmodified allergen and adjuvant such as Ribi adjuvant is useful in desensitization therapy because it enhances the host immune response to any allergen (See claims 22 and 25 of '862 patent, column 4, lines 19-21 and 30-33, sentence spanning from column 7 bridging column 8, in particular). *In re Kerkhoven*, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). Claim 16 is included in this rejection because glutaraldehyde is a species of dialdehyde. The recitation of unmodified allergen or allergen extract(s) is an obvious variation of the teachings of the WO 96/34626 publication because all initial crosslinked (modified) allergen or allergen extract(s) are all start out with unmodified allergen or allergen extract(s). The enhancing TH1 response over a TH2 response in claim 1 is an inherent functional property of the reference 3-DMPL adjuvant. The inherent functional property of a compound cannot be separated from the compound.

At page 23 second paragraph of the Brief, Appellant submits that the '862 patent does not specify which of the three Ribi adjuvant system is used therein. There is no indication in this

document that "Ribi adjuvant" is 3-DMPL. The '862 patent fails to teach or suggest the use of tyrosine to coat or absorb the flea saliva protein disclosed therein.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

This rejection is made over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892). One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. Although the '862 does not indicate that "Ribi adjuvant" is 3-DMPL, the WO 92/16556 publication teaches 3D-MPL or 3D-monophosphoryl lipid A is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) and from Ribi (see page 24, line 23, in particular). In fact, the specification on page 1, line 1 discloses that 3-DMPL is known from GB2220211 (Ribi). The '862 patent teaches a therapeutic composition comprising unmodified allergen of isolated flea saliva protein and the Ribi adjuvant from Ribi ImmunoChem enhances the immune response to any antigen (See column 42, line 20-35, claims 22 and 24 of '862, in particular). It would have been obvious to substitute the adjuvant as taught by the '862 for the 3D-MPL adjuvant as taught by the WO 92/16556 in combination with a tyrosine in a pharmaceutical comprising tyrosine, unmodified allergen, or modified allergen and 3-DMPL for treating allergy as taught by the WO 96/34626, WO 92/16556, and the '862 patent. One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 92/16556 publication teaches that the adjuvant formulations containing 3D-MPL are able to induce specific T cell responses and improve humoral and effector cell mediated (DTH) immune response where DTH is a TH_1 response (See page 29, lines 8-16, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized allergen is useful for desensitization therapy of allergy sufferers since glutaraldehyde modified allergen reduces the antigenicity of said allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular). The '862 patent teaches unmodified allergen and adjuvant such as Ribi adjuvant is useful in desensitization therapy because the adjuvant enhances the host immune response to any allergen (See claims 22 and 25 of '862 patent, column 4, lines 19-21 and 30-33, sentence spanning from column 7 bridging column 8, in particular). *In re Kerkhoven*, 205USPQ 1069 (CCPA 1980),

recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

At page 23 third paragraph of the Brief, Appellant submits that because neither reference teaches or suggests the use of tyrosine, it follows that the ordinary artisan would not arrive at the claimed invention solely by reading the disclosure of WO92/16556 and the '862 patent.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine combined with a modified allergen or allergen extract(s) of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized pollen allergen was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

Claims Rejection - 35 USC § 103

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892) as applied to claims 1-2, 6-8, and 15-17 and 19-23 mentioned above and further in view of Marsh et al (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892).

The paragraph bridging page 23 and 24 of the Brief asserts that because claim 1 is not rendered obvious by the combination of WO92/15665 and the '862 since the WO/34626 patent is

being disqualified as prior art, it follows that claim 18 cannot be rendered obvious by the cited combination.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

In contrast to appellant's assertion that the WO/34626 patent is being disqualified as prior art, the WO96/34626 reference was published November 1996, which is more than one year prior to the effective filing date 4/3/1998 of the instant application. The WO96/34626 reference is a statutory bar under 35 U.S.C. 102(b) and thus cannot be overcome by declaration under 37 CFR 1.131.

At page 24 second paragraph of the brief, Appellant submits that WO 92/15665 and the '892 patent fails to teach or suggest the use of tyrosine. The '110 Patent does not teach or suggest the use of tyrosine in the disclosed vaccine formulation. Hoyne et al. is cited for the teaching that reprogramming of immune responses may be achieved by promoting a Thl response over a Th1 response. While the Hoyne et al. reference provides a great deal of interesting information on the role of interleukins, interferons, cytokines, and CD4+ T cells in the murine and human immune responses, this reference fails to teach or suggest the use of tyrosine or 3-DMPL as compounds to be used in desensitization therapy.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine combined with a modified allergen or allergen extract(s) of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized pollen allergen was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

The WO 92/16556 publication teaches 3D-MPL or 3D monophosphoryl lipid A is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) and is from Ribi (see page 24, line 23, in particular). The reference adjuvant was used to stimulate production of antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH), which is a TH1 immune response (See page 29, lines 8-16, in particular).

The '110 patent teaches various vaccine compositions comprising 3De-acylated monophosphoryl lipid A (3-DMPL), also known as GB2220 211 (See column 1, lines 11-14, in particular). The '110 patent teaches that individual adjuvants such as 3D-MPL and QS21 increase gamma interferon production, however, a combination of adjuvants such as 3D-MPL and QS21 are synergistic for production of CTL and gamma interferon responses more than twice the sum of individual response (See column 5, lines 16-22, in particular).

Hoyne *et al* teach T helper 1 (Th1) cells preferentially secrete cytokines (i.e., IFN-γ) whereas Th2 cells preferentially secrete IL-4 and IL-10. The IFN-γ secreted by Th1 cells is known to inhibit growth and differentiation of T helper 2 (Th2) cells and vice versa (See page 180, column 1, Introduction, in particular). Hoyne *et al* teach allergen-specific T cells isolated from atoptic patients show a high level of IL-4 and a low level of IFN-γ (See page 180, column 1, first paragraph, in particular) and patients who have been desensitized normally display a decrease in Th2 immune response. Clinical improvement in allergic patients correlates with a decrease in immediate and late phase skin reactivity with a long-term rise in IgG4 levels and a decrease in allergen specific IgE (See page 183, column 1, last paragraph, in particular). Hoyne *et al* further teach that a major key to successful immunotherapy depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells leads to clinical improvement usually correlates with a decreases in allergen specific IgE, a decrease in immediate and late phase skin reactivity and a rise in IgG4 level in human (See page 183, column 2, last paragraph, in particular). Vaccination under conditions such as co-administering allergen in the presence of IFN-γ to promote Th1 responses instead of Th2 responses may reprogrammed the immune response to prevent allergic sensitization (See abstract, page 183, column 2, Future directions, in particular).

At page 24 second paragraph of the brief, Appellant submits that because none of the cited references alone or in combination teach or suggest the essential element of tyrosine as a component of a composition used for desensitization therapy against unmodified allergen, the

rejection of claim 18 as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892) as applied to claims 1-2, 6-8, and 15-17 and 19-23 mentioned above and further in view of Marsh et al (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892) should be withdraw.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine and a modified allergen or allergen extract(s) of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches the reference pharmaceutical composition was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

Claims Rejection - 35 USC § 103

Claims 1 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of Holen *et al* (Clin Exp Allergy 26(9):1080-8, Sept 1996; PTO 892), WO 92/16556 (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892).

At paragraph bridging page 24 and 25 of the brief, Appellant submits that claim 23 depends from claim 1. With the disqualification of the primary reference WO 96/34626, this rejection must based solely upon the teachings of the secondary references. Holen reference fails to teach or suggest the use of tyrosine or 3-DMPL. The WO92/16556 fails to teach or suggest tyrosine as a compound useful in the modulation of immune response. Similarly the '110 patent fails to teach or suggest the addition of tyrosine to the disclosed formulation. Lastly, Hoyne et al reference fails to teach or suggest tyrosine or 3-DMPL as beneficial regulators of immune response. Because none of the cited references alone or in combination teach or suggest a

combination of tyrosine, 3-DMPL and grass pollen or ovalbumin allergen or allergens, it follows that claims 1 and 23 are not rendered obvious by the cited combination of references.

Appellant' arguments and the declaration of Alan Worland Wheeler filed 9/15/03 have been fully considered but are not found persuasive.

In response to Appellant' argument that the primary reference WO 96/34626 is disqualified as prior art, the WO96/34626 reference was published November 1996, which is more than one year prior to the effective filing date 4/3/1998 of the present application. The WO96/34626 reference is a statutory bar under 35 U.S.C. 102(b) and thus cannot be overcome by declaration under 37 CFR 1.131. Therefore, the WO96/34626 reference is not being disqualified as prior art.

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine combined with a modified allergen or allergen extract(s) of glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D. fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference tyrosine is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized pollen allergen was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

The invention of claim 1 differs from the teachings of the reference in that the pharmaceutical composition selectively enhances a TH1 response over a TH2 response comprising 3-DMPL.

The invention of claim 23 differs from the teachings of the reference only in that the composition of allergen or allergen extracts is ovalbumin.

Holen *et al* teach proteins of hen egg whites are common ingredients in food and difficult to eliminate. Allergens of egg white induce allergic symptoms among relatively high number of patients suffering from food allergy. Holen *et al* teach human T cells from allergic patients recognized several allergens such as ovomucoid, lysozyme and ovalbumin and epitopes within the ovalbumin such as 105-122 and 323-339 (see abstract, in particular). Ovomucoid and ovalbumin induced allergen specific IgE synthesis by even a small fraction of B cells present in

the ovalbumin and ovomucoid specific T cell lines. Holen *et al* further teach that OA peptides 105-122 and 323-339 have no affinity to the specific IgE of the two patients, which could be useful for peptide-based immunotherapy.

The WO 92/16556 publication teaches 3D-MPL is a known adjuvant used in vaccine (see page 7, lines 8-11, in particular) and is from Ribi (see page 24, line 23, in particular). The reference adjuvant is useful for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH), which is a TH1 immune response (See page 29, lines 8-16, in particular).

The '110 patent teaches various vaccine compositions comprising 3De-acylated monophosphoryl lipid A (3-DMPL), also known as GB2220 211 (See column 1, lines 11-14, in particular). The '110 patent teaches that individual adjuvants such as 3D-MPL and QS21 increase gamma interferon production, however, a combination of adjuvants such as 3D-MPL and QS21 are synergistic for production of CTL and gamma interferon responses more than twice the sum of individual response (See column 5, lines 16-22, in particular).

Hoyne *et al* teach T helper 1 (Th1) cells preferentially secrete cytokines (i.e., IFN-γ) whereas Th2 cells preferentially secrete IL-4 and IL-10. The IFN-γ secreted by Th1 cells is known to inhibit growth and differentiation of T helper 2 (Th2) cells and vice versa (See page 180, column 1, Introduction, in particular). Hoyne *et al* teach allergen-specific T cells isolated from atoptic patients show a high level of IL-4 and a low level of IFN-γ (See page 180, column 1, first paragraph, in particular) and patients who have been desensitized normally display a decrease in Th2 immune responses. Clinical improvement in allergic patients correlates with a decrease in immediate and late phase skin reactivity with a long-term rise in IgG4 levels and a decrease in allergen specific IgE (See page 183, column 1, last paragraph, in particular). Hoyne *et al* further teach that a major key to successful immunotherapy depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells leads to clinical improvement usually correlates with a decrease in allergen specific IgE, a decrease in immediate and late phase skin reactivity and a rise in IgG4 level in human or IgG2a or IgG2b in mouse (See page 183, column 2, last paragraph, in particular). Vaccination under conditions such as co-administering allergen in the presence of IFN-γ to promote Th1 responses instead of Th2 responses may reprogrammed the immune response to prevent allergic sensitization (See abstract, page 183, column 2, Future directions, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the allergen or allergen extract(s) as taught by the WO 96/34626 publication for the ovalbumin as taught by the Holen *et al* in a pharmaceutical composition comprising tyrosine and ovalbumin in combination with adjuvant such as 3-DMPL that is capable of enhancing a Th1 response over a TH2 response as taught by the WO 92/16556 publication, the '110 patent and Hoyne *et al.* From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the references because Holen *et al* teach ovalbumin is one of the allergens in egg white that induces allergic symptoms by increasing allergen specific IgE synthesis among relatively high number of patients suffering from food allergy (see abstract, in particular). The WO 92/16556 publication teaches that the adjuvant formulations containing 3D-MPL induce specific T cell responses such as a DTH immune response, which is a TH1 response (See page 29, lines 8-16, in particular). Hoyne *et al* teach that a major key to successful immunotherapy depends on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells leads to clinical improvement usually correlates with a decrease in allergen specific IgE, a decrease in immediate and late phase skin reactivity and a rise in IgG4 level in human (See page 183, column 2, last paragraph, in particular). Vaccination under conditions such as co-administering allergen in the presence of IFN-γ to promote Th1 responses instead of Th2 responses may reprogrammed the immune response to prevent allergic sensitization (See abstract, page 183, column 2, Future directions, in particular). The '110 patent teaches that individual adjuvants such as 3D-MPL and QS21 increase gamma interferon production, which is a Th1 response (See column 5, lines 16-22, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized pollen allergen was used in desensitization therapy of allergy sufferers for the advantage of glutaraldehyde modified allergen reduced allergenicity of allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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May 1, 2004

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